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#13 Appeal brief(3)

Docket No.: 50198-154 PATENT

8.4.03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of :

Trevor DOUGLAS, et al. :

Application No.: 09/734,206 : Group Art Unit: 1648

Filed: December 12, 2000 : Examiner: J. Parkin

For: NANOSCALE PARTICLES SYNTHESIZED WITHIN AN ASSEMBLED VIRION

TRANSMITTAL OF APPEAL BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith in triplicate is Appellants' Appeal Brief in support of the Notice of Appeal filed July 29, 2003. Please charge the Appeal Brief fee of $320.00 to Deposit Account 500417.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,
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APPEAL BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an Appeal to the Board of Appeals and Interferences of the United States Patent and Trademark Office under 37 CFR § 1.191 for the above-identified patent application. Three copies of this Appeal Brief are filed herewith along with the requisite fee under 37 CFR § 1.17(c), $320.00, to be charged to Deposit Account 500417. Appellants herein appeal from claims that have been twice rejected pursuant to 37 CFR § 1.191(a).

Real Party In Interest

This application is assigned to The Research and Development Institute, Inc., by assignment recorded on April 30, 1997, at Reel 8584, Frame 0340.

Related Appeals and Interferences

There are no related appeals or interferences.

Status of the Claims

Claims 21-29 and 31-38 are pending herein. No claims are allowed. An amendment has been filed with this Appeal Brief: (i) to cancel claim 30 because a cowpea chlorotic mottle virus coat protein is not a non-plant virion coat protein, (ii) to amend claim 26 to correct misspelled words and to delete the redundant term "Protozoan," and (iii) to amend claim 38 to correct the spelling of "glyco protein." Since the rejection of the claims is not final, the amendment should be entered as a matter of right. Accordingly, a copy of claims 21-29 and 31-38, which are on appeal, are found in the APPENDIX. The claims as set forth in the APPENDIX include the amendments to claims 22 and 25 made during prosecution and the amendments to claims 26 and 38 as set forth above.

Status of Amendments

All amendments filed prior to filing the amendment with this Appeal Brief have been entered. The amendment filed with this Appeal Brief to cancel claim 30 and amend claims 26 and 38 should be entered as a matter of right since the rejection of the claims is not final.

Summary of the Invention

The invention is directed to novel virion constrained nanoscale particles and process for producing the same. In particular, the invention related to virion-constrained nanoparticles comprising an inorganic, organic and/or organo-metallic material surrounded by a shell of one or more virion coat proteins.

Ultrafine particles have been prepared using an apoferritin shell and an inorganic core. Ferritin is a protein, but the size of the particles is constrained by the size of the ferritin cavity. The internal cavity of the ferritin is restricted to 8 nm or less. Large molecules may not readily enter the protein. The present invention overcomes the restrictions and limitations of these ultrafine particles.

The invention provides virion-constrained nanoparticles, characterized by a homogeneous particle size distribution and homogeneous particle shape, the particles comprising an organic, inorganic and/or organo-metallic material surrounded by a shell of virion coat protein.

The invention additionally provides for a method of making virion-constrained nanoparticles, comprising the steps of:

a) providing isolated and substantially purified animal virion coat protein shells containing controllable gates;

b) incubating the virion coat protein shell in a solution comprising one or more organic, inorganic, and/or organometallic materials under conditions that permit controlled entry of the materials into the virion shell;

c) adjusting the solution conditions in such a manner that the virion coat protein shell entraps the materials of step b); and

d) isolating the virion-constrained nanoparticles produced.

Issues

1. Claims 21-29 and 31-38 stand rejected under the written description requirement of 35 U.S.C. §112, first paragraph. The issue is whether the disclosure of the application reasonably conveys to the a person skilled in the art that the inventors had possession of the claimed subject matter as of the effective filing date of the application.

2. Claims 21-29 and 31-38 stand rejected as not being enabling under the first paragraph of 35 U.S.C. § 112. The issue is whether a person skilled in the art could make and use the virion-constrained nanoparticles and the process for producing the same as recited in claims 21-29 and 31-38 from the disclosures in the specification coupled with information known in the art, without undue experimentation.

Grouping of Claims

Appellants respectfully submit that with respect to each rejection under 35 U.S.C. § 112, first paragraph, claims 22-25 stand or fall with claim 21 and that claims 31-33 and 36-38 stand or fall with claim 29. Claims 21, 26-29, 34 and 35 do not stand or fall together for the reasons set forth in the arguments below.

Argument

Claims 21-29 and 31-38 stand rejected as not complying with the written description and enablement requirements of the first paragraph of 35 U.S.C. § 112. It is well settled that the written description and enablement requirements of the first paragraph of 35 U.S.C. § 112 are separate and distinct from one another and have different tests. *See In re Wilder*, 736 F.2d 1516, 1520, 222 USPQ 369, 372 (Fed. Cir. 1984); *In re Barker*, 559 F.2d 588, 591, 194 USPQ 470, 472 (CCPA 1977); *In re Moore*, 439 F.2d 1232, 1235-1236, 169 USPQ 236, 239 (CCPA 1971).

Rejection for Lack of Written Description

Claims 21-29 and 31-38 stand rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention." According to the Examiner:

> The claims are directed toward virion-constrained nanoparticles comprising a non-plant virion coat protein shell surrounding a nanoparticle of non-viral origin. The disclosure provides *in vitro* methods for reassembling CCMV [cowpea chlorotic mottle virus] plant viral coat proteins into empty particles. These particles were incubated with 0.4 M Na_2WO_4 to produce plant virion-constrained nanoparticles. Additional methods detailing the preparation of empty CCMV plant virions followed by their incubation with WO_4^{-2} ions under conditions of varying pH, to allow controlled gating, were also provided. The disclosure fails to describe the preparation of virion-constrained nanoparticles employing animal virion coat proteins.

The Examiner asserts that "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). The Examiner states that "[t]he issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of nanoparticles comprising non-plant virion coat proteins." The main focus of the Examiner is that Appellants did not disclose a working example for forming a virion-constrained nanoparticle using a non-plant or animal virion coat protein.

The present specification, as well as the specification of the parent application, does not disclose, imply or even suggest that the process for producing a virion-constrained nanoparticle using a non-plant or animal virion coat protein shell is substantially different from the process for producing a virion-constrained nanoparticle using a plant virion coat protein shell. The virion-constrained nanoparticle and process of making the same using a plant virion was issued as U.S. Patent No. 6,180,389 B1 on January 30, 2001. The patent is based on Application No. 08/775,366 filed January 3, 1997, which is the parent of the present application.

Claims 21-25, 29, 31-33 and 36-38 find written description support at page 11, line 20 to page 13, line 18 and page 17, line 25 to page 21, line 19 of the specification and in the original claims. The specification supports non-plant or animal virions such as prokaryotic, protozoan and eukaryotic viruses and virus-like particles as well as bacteriophage virions. These species are set forth in claims 26 and 34, and are supported in the specification at page 14, lines 1-9. Prokaryotic viruses are set forth in claims 27 and 35 and include Plasmaviridae, SSv1 group viruses, Lipothrixviridae, Cystoviridae, Corticoviridae, Myoviridae, Siphoviridae, Podoviridae, Microviridae, Inoviridae and Leviviridae. These species find written description support at page 14, lines 4-7 in the specification. Claim 28 recites eukaryotic virions as including Poxviridae, Entomopoxyviridae, Baculoviridae, Eubaculovirinae, Nudibaculovirinae, Polydnaviridae, Ichnovirus, Iridoviridae, Bracovirus, Parvoviridae, Flavivirdae, Tagviridae, Bunyaviridae, Rhabdoviridae, Reoviridae, Bimaviridae, Picornaviridae, Tetraviridae and Nadoviridae. These species find written description support in the paragraph bridging pages 14 and 15 of the specification. Accordingly, at least with respect to claims 26-28, 34 and 35, the specification describes the invention in the same terms as the claims. Thus, nothing more is required for compliance with the description requirement of the first paragraph of 35 U.S.C. § 112. *See In re Gardner*, 475 F.2d 1389, 1391, 177 USPQ 396, 397, *supplemental opinion*, 480 F.2d 879, 879-880, 178 USPQ 149 (CCPA 1973); *In re Smith*, 481,F.2d 910, 914, 178 USPQ 620, 624 (CCPA 1973). As for the remaining claims on appeal, claims 21-25, 29, 31-33 and 36-38, except for the reciting the virion as being "animal" or "non-plant" the claims are substantially identical to the

original claims and the specification. These claims also in compliance with the written description requirement of 35 U.S.C. § 112, first paragraph. *See In re Bowen*, 492 F.2d 859, 864 181 USPQ 48, 52 (CCPA 1974).

The Examiner concedes that Appellant "shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." However, the Examiner contends that the "claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function." In particular, the Examiner specifically asserts that the specification fails (i) "to describe the isolation and purification of non-plant viral coat proteins," (ii) "to detail the preparation of virion-constrained nanoparticles comprising these virions," and (iii) "to describe the loading of any given animal virion-constrained nanoparticle with various organic, inorganic, and organometallic materials." In addition, the Examiner asserts that "the state-of-the-art vis-à-vis the preparation of virion-constrained nanoparticles is one of unpredictability" and that

> the skilled artisan would reasonably conclude that applicants were not in possession of the claimed invention at the time of filing. Applicants are further advised that a long laundry list merely referencing other viral animal viruses does not constitute a proper written description of every species in the genus since it fails to lead the skilled artisan to any particular animal viral coat protein.

The function of the 35 U.S.C. § 112, first paragraph, written description requirement, is that the specification reasonably convey to a person of ordinary skill in the art that, as of the filing date of the application, the inventors had possession of the subject matter later claimed. *In*

re Edwards, 568 F.2d 1349, 1351, 196 USPQ 465, 467 (CCPA 1978); *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976); *In re Lukach*, 442 F.2d 967, 969, 169 USPQ 795, 796 (CCPA 1971). The determination as to whether the specification provides support for the newly claimed subject matter is primarily factual and depends on the nature of the invention and the amount of knowledge imparted by the disclosure to those of ordinary skill in the art. *In re Wertheim*, 541 F.2d at 262, 191 USPQ at 96.

The invention as claimed is supported by the written description as discussed *supra*. The arguments by the Examiner are directed more to the enablement requirement, than to the written description requirement. However, Appellants respond as follows to the Examiner's arguments.

A person skilled in the art, after reading the specification, would know the non-plant or animal virions that may be used to prepare the nanoparticles. Specific species of the prokaryotic, protozoan and eukaryotic viruses are clearly set forth in the written description of the invention as discussed *supra.* From the written description, a person skilled in the art would be able to immediately envisage the product claimed from the disclosed process. The product is a nanoparticle comprising non-plant or animal virion coat protein surrounding an organic, inorganic or organo-metallic material or particle. The process for making the nanoparticle would be immediately apparent to a person skilled in the art. While the only two examples in the specification for preparing a virion constrained nanoparticle are directed to using a plant virion, a person skilled in the art would have been led from a reading of the specification that a substantially similar process could be employed using a non-plant or animal virion, and that the inventors had possession of the claimed subject matter as of the effective filing date of the

application. The detailed processes for both plant and animal virions are disclosed at pages 17-20 of the specification.

The Examiner finds that the disclosure lacks a written description of how to isolate and purify the non-plant viral coat proteins. This is a conclusionary statement, not supported by evidence. The Examiner has not explained or presented cogent reasoning as to why it is necessary for the present application to describe the isolation and purification of non-plant viral coat proteins for a person having ordinary skill in the art to practice the invention without undue experimentation. The Examiner has not presented any evidence to establish why such a person would not have recognized that, at the time of filing the application, the inventors had possession of the claimed subject matter.

Contrary to the position taken by the Examiner, the written description does set forth details of the preparation of virion-constrained nanoparticles comprising non-plant or animal virions. The specification further describes the loading of various organic, inorganic, and organometallic materials into said virions. The specification describes the processes or methods at pages 11-13 and at page 17, line 25 to page 19, line 18 and in original claims 10-20. The processes or methods disclosed in this written disclosure would apply to both plant and non-plant virions. The process disclosed comprises the steps of (i) providing isolated and substantially purified animal virion coat protein shells containing controllable gates, (ii) incubating the virion coat protein shell in a solution comprising one or more organic, inorganic, and/or organometallic materials under conditions that permit controlled entry of the materials into the virion shell, (iii) adjusting the solution conditions in such a manner that the virion coat protein shell entraps the materials of step (ii), and (iv) isolating the virion-constrained nanoparticles produced. From this

disclosure, a person having ordinary skill in the art would have recognized that, at the time of filing the application, the inventors had possession of the claimed subject matter.

The Examiner asserts that "the preparation of virion-constrained nanoparticles is one of unpredictability." This is a conclusionary statement, and not supported by evidence. No evidence has been presented by the Examiner to establish that a person having ordinary skill in the art would not have recognized that, at the time of filing the application, the inventors did not have possession of the claimed subject matter because of "unpredictability."

The Examiner suggests that Appellants "may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole." The statement is conclusionary. The rejection fails to present an explanation or cogent reasoning as to why such a showing would be necessary in the present application for a person having ordinary skill in the art to reasonably conclude that the Appellants were not in possession of the claimed subject matter as of the effective date of the filing of the application, unless there was detailed disclosure of drawings or structural chemical formulas.

The Examiner suggested that Appellants "may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Again, this is a conclusionary statement, not supported by evidence. The rejection fails to explain why the complete or partial structures of the non-plant virions, as well

as their physical and chemical properties including a functional characteristics, would be necessary for a person having ordinary skill in the art to reasonably conclude that the Appellants were not in possession of the claimed subject matter as of the effective filing date of the application.

The Examiner asserts that for "some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight" are required. Again, this is a conclusionary statement, not supported by evidence. The rejection fails to explain why the a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight of the non-plant virions would be necessary for a person having ordinary skill in the art to reasonably conclude that the Appellants were not in possession of the claimed subject matter as of the effective filing date of the application.

The Examiner further asserts that the "written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function" and that "[w]ithout such a correlation, the capability to recognize or understand the structure form the mere recitation of function and minimal structure is highly unlikely." According to the Examiner, "[f]actors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." The statements by the Examiner are conclusionary, and not supported by evidence. The rejection fails to relate these factors to the claimed invention and explain why, in

the absence of these factors, a person having ordinary skill in the art would have reasonably concluded that Appellants were not in possession of the claimed invention at the time of filing.

For all of the foregoing reasons, the claimed subject matter recited claims 21-29 and 31-38 satisfy the written description requirement of the first paragraph of 35 U.S.C. § 112. Accordingly, it is respectfully requested that the rejection of claims 21-29 and 31-38 under 35 U.S.C. § 112, first paragraph, as lacking written description, be reversed.

Rejection for Lack of Enablement Requirement

Claim 21-38 stand rejected under 35 U.S.C. §112, first paragraph, as being based upon a non-enabling disclosure. According to the Examiner, the disclosure "does not reasonably provide enablement for compositions containing virion-constrained nanoparticles comprising a shell of a non-plant virion coat protein or methods of their preparation."

The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation. *United States V. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989); *In re Stephens*, 529 F.2d 1343, 1345, 188 USPQ 659, 661 (CCPA 1976). The determination of enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1573, 224 USPQ 409, 411 (Fed. Cir. 1984). In determining whether a disclosure would require undue experimentation to make the claimed subject matter, the Examiner must consider the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of

the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988), citing with approval *Ex parte Forman*, 230 USPQ 526, 547 (Bd. Pat. App. & Int. 1986). The burden is on the Examiner to establish a reasonable basis to question the adequacy of Applicants' disclosure. *In re Marzocchi*, 439 F.2d 220, 223-224, 169 USPQ 367, 370 (CCPA 1971).

The specification states at page 16, lines 9-10 that the "invention is exemplified below using the coat protein of the cow pea chlorotic mottle virus ...." The examples presented in the specification are only exemplary. The specification identifies specific plant and non-plant virions that can be used for making nanoparticles. The specification further discloses method or process steps for making the nanoparticles at pages 17-20 of the specification. The disclosed process applies to using a plant virion or an animal virion. Accordingly, a person having ordinary skill in the art upon reading the specification would have found that the processes would apply to both plant and animal virions, notwithstanding the fact that the only two examples in the specification are directed to the cowpea virus.

The Examiner noted the *Wands* factors and made a finding that undue experimentation would be required because (i) "the disclosure fails to provide adequate guidance pertaining to the identification, isolation, and purification of suitable non-plant viral proteins that can reasonably be expected to function in the desired manner," (ii) "the disclosure fails to provide a single working embodiment involving a non-plant virion coat protein and the subsequent loading and unloading of said nanoparticle," (iii) "the claims are of excessive breadth and encompass a large genus of genotypically and phenotypically diverse non-plant viruses," and (iv) "the state-of-the-

art vis-à-vis the preparation of non-plant virion-constrained nanoparticles is one of unpredictability." It is Appellant's position that the Examiner has not established a *prima facie* case for a finding of lack of enablement and that one skilled in the art could make or use the claimed invention from the disclosures in the specification, coupled with information known in the art, without undue experimentation.

The method of the claimed invention is quite simple. The first step is to provide an isolated and substantially pure coat protein of the non-plant virion. The second step is to incubate the protein in a solution comprising the material to be entrapped in the coat protein. The third step is to provide conditions in which the nanoparticles are surrounded by the protein. The last step is to isolate the virion-constrained nanoparticles. The Examiner contends that the invention is not simple, but includes "a number of factors that can complicate the preparation of non-plant virion-constrained nanoparticles including, *inter alia*, the physicochemical properties of the coat protein (which influence particle size, shape, number, and surface charge), drug loading, drug release, nanoparticle toxicity, and nanoparticle immunogenicity." The argument is conclusionary, and lacks evidence for support. The rejection fails to explain how each of the aforementioned factors is related to steps in the claimed process. The Examiner has not shown how these factors would necessarily require that a person having ordinary skill in the art to engage in undue experimentation to practice the claimed invention.

The Examiner asserts that "the disclosure fails to provide adequate guidance pertaining to the identification, isolation, and purification of suitable non-plant viral proteins that can reasonably be expected to function in the desired manner." In support of this argument, the Examiner contends that claims encompass "an exceedingly large genus of non-plant viruses."

Specific non-plant or animal virions are disclosed on pages 14 and 15 of the specification and are recited in claims 26-28 and 34 and 35 as discussed *supra*. These specific virions support the genus recited in claim 21-25, 29, 31-33 and 36-39. The rejection fails to set forth any reasoning that would explain why a person having ordinary skill in the art, based on the disclosure of the specific non-plant or animal virions, would have had to engage in undue experimentation to practice the claimed invention. The Examiner further asserts that the "disclosure fails to describe the isolation, purification, and preparation of virion-constrained nanoparticles comprising any of the aforementioned non-plant viral coat proteins." This is a conclusionary statement lacking any evidentiary support. A mere conclusion is not supported by evidence of record in this patent application. *In re Thrift*, 298 F.3d 1357, 63 USPQ2d 2002, (Fed. Cir. 2002). There is no explanation as to why a person having ordinary skill in the art would require disclosure of the isolation, purification and preparation the non-plant viral proteins in order to practice the claimed invention without undue experimentation. The Examiner maintains that a "[p]roper virion assembly often requires an orchestrated interaction between both viral and cellular proteins." As evidence to support this conclusion, the Examiner relies on an article by Dong et al. According to the Examiner, Dong et al. disclose that the "nature of protein-protein interactions during retrovirus assembly is not well understood, and molecular genetic analyses of functional regions within the gag and env gene products are only beginning to provide information in this regard." The Examiner has not explained (i) how the lack of understanding of the nature of protein-protein interactions during retrovirus assembly relate to encapsulation using a non-plant virion and why such lack of understanding would require undue experimentation by a person having ordinary skill in the art and (ii) how the gag and env gene products referred to would render non-

enabling the encapsulation of an organic or inorganic material by a non-plant virion. The Dong et al. reference refers to mechanisms involving viral and cellular proteins, but the Examiner has not explained by cogent scientific reasoning how the lack of understanding of these mechanisms would have led to undue experimentation to practice the present invention.

Copies of the Declarations Under 37 CFR § 1.132 by Adam Zlotnick, Ph.D., Thomas J. Smith, Ph.D., and John E. Johnson, Ph.D., which were filed in the parent of this application (Application No. 08/775,366), are attached as APPENDIX B to the Amendment and Request for Reconsideration filed on January 9, 2003 in the present application. Each of the declarants are skilled in the art (Zlotnick, p. 2, ¶ 5; Smith, p. 3, ¶ 5; and Johnson, p. 3, ¶ 5) and declare that

> the Examiner also refers to a publication by Dong et al. ..., as suggesting that the prior art teaches that the mechanisms of viral assembly are complex and poorly understood. This publication was made in 1993, well prior to the filing of this patent application. This patent application presents a clear description of how controlled gating may be used. It is clear that Dong had no concept of the gating mechanism of this invention and should not be used as evidence to raise questions about the gating mechanism of this invention because Dong et al. is not concerned with the same processes. Once again, the claims of the inventors are not addressing the multitude of viral assembly mechanisms. They claim only that given a stable empty viral protein cage to which there is access to the virion's interior that it can be used as a constrained reaction vessel for selective material entrapment. [Zlotnick Declaration, p. 9, ¶ 13; Smith Declaration, p. 9, ¶ 13; and Johnson Declaration, p. 9, ¶ 13.]

Dong et al. does not represent the state of the art as of the effective date of filing of the present application, namely, January 3, 1997. The reference was published in 1993, four years before the filing of Applicants' effective filing date. Therefore, Dong et al. is not sufficient evidence to establish, as of the effective filing date of the present application, the state of the art was that proper virion assembly often required an orchestrated interaction between both viral and cellular proteins. The Examiner further states:

> The specification does not describe the preparation of virion-constrained nanoparticles from any other virus, excluding CCMV. However, the broadly recited claim language applies to a multitude of viral coat proteins, many whose role in virion assembly remains to be elucidated, obtained from any prokaryotic, eukaryotic, plant, protozoan, or virus-like particles. However, applicants have not set forth sufficient guidance in the specification pertaining to the identification or selection [of] suitable viral coat proteins, purification protocols, reassembly protocols, gating conditions, and delivery procedures."

Again, this is a conclusionary statement, not supported by any evidence. Appellants have identified specific non-plant virions that can be used in the invention. See pages 14 and 15 of the specification and in the original claims. They have also disclosed the processes for forming the nanoparticles on pages 17-20 of the specification. The Examiner has not presented any evidence or cogent reasoning as to establish that the role in virion assembly remains to be elucidated such that a person having ordinary skill in the art would not have been able to practice the claimed invention without undue experimentation. The Examiner has also not explained why such a person would necessarily require information regarding purification protocols, reassembly protocols, gating conditions, and delivery procedures in order to practice the invention, without undue experimentation.

The Examiner argues that "the disclosure fails to provide a single working embodiment involving a non-plant virion coat protein and the subsequent loading and unloading of said nanoparticle." The Examiner contends that the "disclosure fails to describe the preparation of a virion-constrained nanoparticle comprising a non-plant virion coat protein and the subsequent loading and unloading of said nanoparticle." It appears to be the Examiner's position that the specification must include a working example of a non-plant virion. Such a working example is not required to establish enablement. *See In re Strahilevitz,* 668 f.2d 1229, 212 USPQ 561

(CCPA 1982) (working examples are desirable, but not necessarily required to satisfy enablement requirement). An inventor need not explain every detail of the invention. Patents are not production documents, and nothing in the patent law requires that the inventors disclose examples for each and every virion that is disclosed in the specification. *See DeGeorge v. Vernier*, 768 F.2d 1318, 226 USPQ 758 (Fed. Cir. 1985); *Christianson v. Colt Industries Operating Corp.*, 822 F.2d 1544, 3 USPQ2d 1241 (Fed Cir 1987). A Declaration by Michael J. Young, which is of record in parent Application No. 08/775,366, is attached as APPENDIX E to the Amendment and Request for Reconsideration filed January 9, 2003, in the present application. Dr. Young's declaration at page 2, ¶ 4 states that all virus (both plant and animal) form a protein shell. The declaration further states at page 3, ¶ 4 that both plant and animal viruses all have a β barrel jelly roll fold that appears to provide the structure for viral capsids to act as constrained reaction vessels for entrapment of inorganic, organic and metallo-organic substances. The declaration further states at page 4, ¶ 4 that both plant and animal virions have holes that allow access from outside to inside the virion interior. Example 1 of the specification which describes the synthesis of a paratungstate polymer within a cow pea virus. The Young Declaration at page 5, ¶ 6 describes incubating animal (Norwalk) virion particles 25mM Na_2WO_4 to produce plant virion-constrained nanoparticles. Therefore, contrary to the Examiner's argument, the disclosures would describe the preparation of virion-constrained nanoparticles using animal virions and would provide sufficient guidance to enable a person having ordinary skill in the art to practice the invention without undue experimentation.

The Examiner argues that "the claims are of excessive breadth and encompass a large genus of genotypically and phenotypically diverse non-plant viruses." Claims 26-28, 34 and 35

recite specific non-plant virions, and therefore, are not excessively broad. The large number of specific non-plant or animal virions are disclosed at pages 14 and 15. The large number disclosed would support the scope of the genus recited in claims 21-25, 29, 31-33 and 36-39 such that a person having ordinary skill in the art would not have been required to engage in undue experimentation to practice the claimed invention.

The Examiner argues that "the state-of-the-art vis-à-vis the preparation of non-plant virion-constrained nanoparticles is one of unpredictability." The Examiner made a finding that the field of molecular nanotechnology is in its infancy, and presumably is unpredictable, such that a person having ordinary skill in the art would have to engage in undue experimentation to encapsulate organic and inorganic materials using a non-plant virion. For this finding, the Examiner relies on an article published by Kaehler in 1994. According to the Examiner, Kaehler "reviews the state-of-the-art and concludes that while there are many potential applications for nanotechnology, these applications have yet to be realized." The reference only establishes the state of the art in 1994, and not the state of the art or level of skill in the art in January 3, 1997, the effective filing date of the present application. Moreover, a field being in its infancy is not, in and of itself, sufficient to establish that a person having ordinary skill in the art would been required to engage in undue experimentation to practice the processes disclosed in the application. The Examiner refers to the limited number of applications in nanotechnology. The applications in nanotechnology are not the issue here. The issue is whether the non-plant virions will encapsulate organic, inorganic or organometallic material. The state of the art that has been presented by the Examiner does not establish a state of the art that virions are unpredictable and that non-plant virions would be expected to perform substantially differently from non-plant

animal virions. The Examiner has not presented any evidence to establish that a person skilled in the art following the method steps outlined on page 17-20 of the specification could not practice the invention without undue experimentation. The Examiner further relies on an article by Douglas et al. published in 1987. This article discusses the state of the art in 1987 which is 10 years before the effective filing date of the present application. It is Appellants' position that the combined teachings of Dong et al., Kaehler and Douglas (1987) fail to establish the state of the art or level of skill in the art as of the effective 1997 filing date of the present patent application.

The Examiner relies on an article by Douglas published in 1996 as providing "an overview of the biomimetic synthesis of nanoscale particles in organized protein cages." The Examiner asserts that the reference discloses that a number of limitations have precluded advancement of the technology, namely, "instability to particle aggregation, inhomogeneous particle size distributions, insolubility of hosts matrices, and an inability to extract the material from the host matrix." The claims are directed to a virion-constrained nanoparticle comprising a non-plant virion coat protein shell surrounding a nanoparticle and a process for producing the same. The Examiner has not explained how and why particle aggregation, inhomogeneous particle size distributions, insolubility of host matrices and the inability to extract the material from the host matrix would render the claimed subject matter non-enabling and why a person having ordinary skill in the art would be required to engage in undue experimentation to practice the claimed invention. It is unclear why the inability to extract the material from the host matrix is relevant to the claimed subject matter since the claims are not directed to extracting the encapsulated material. Also, the rejection lacks any explanation based on scientific reasoning as to why and how particle aggregation, particle size and insolubility of host matrices are relevant to

the claimed method of making an protein encapsulated nanoparticle or to the claimed virion constrained nanoparticle, and why such factors would lead to undue experimentation.

As set forth *supra*, Declarants Zlotnick, Smith and Johnson are persons skilled in the art. Their declarations are evidence that the limitations referred to by the Examiner would not require undue experimentation to practice the claimed invention. With respect to the 1996 Douglas publication, each of the declarants states that

> the Examiner, ... refers ... to the publication by Douglas ... (1996), as indicating that a number of limitations have precluded the advancement of synthesis of nanoscale particles into organized protein cages. This is the inventor Trevor Douglas's own publication and simply indicates on page 92 some difficulties to overcome problems with instability to particle aggregation and the like. However, this publication was made before the inventors completed their invention. There is evidence in the record from Dr. Douglas which clearly refutes these earlier writings. The Examiner therefore is relying on the publication by the inventor made before the invention was made. This publication is overcome by the inventors' representation in this patent application and Dr. Douglas's Declaration of record. [Zlotnick, p. 8, ¶ 11; Smith, p. 8, ¶ 11; and Johnson, p. 8, ¶ 11.]

The Douglas Declaration, which was of record in parent Application No. 08/775,336, is attached as APPENDIX D to the Amendment and Request for reconsideration filed on January 9, 2003 in the present application. In his declaration, Douglas states that "it is my scientific opinion that the subject invention represents a general method for encapsulating a wide variety of organic and inorganic material within the interior cavities of both RNA-containing and RNA-depleted virions without undue experimentation" (Douglas Declaration, p. 3, ¶ 5). The record of this application does not present any evidence to cast doubt that Douglas' statement or aforementioned statement from Declarants Zlotnick, Smith and Johnson are not true.

The Examiner also relies on Howk et al. published in 1996 as teaching the state of the art as of the effective filing date of the present application. According to the Examiner, Howk et al.

"provide several concerns regarding gating control as a control element for nanoparticle loading." Declarants Zlotnick, Smith and Johnson, persons skilled in the art, declare in each of their declarations the following:

> The Examiner ... refers to a publication by Howk et al. ... as disclosing several concerns regarding gating as a control element for nanoparticle loading. While the Examiner points to concerns raised in this article, what is actually concluded in the Abstract is that gating has a critical influence on the ease of formation and stability of host guest complexes and that hosts equipped with gates can form very stable complexes with a variety of guests under readily achievable conditions. Therefore, this publication, relied on by the Examiner as suggesting concerns, actually shows that when used correctly, gating can be used as a control element under readily achievable conditions. Therefore, this article refutes the Examiner's suggestions. [Zlotnick Declaration, p. 8, ¶ 12; Smith Declaration, p. 8, ¶ 12; and Johnson Declaration, p. 8, ¶ 12.]

There is no evidence of record to cast doubt on the truthfulness of this statement in each of the declarations. The Examiner has not explained how why a lack of disclosure to control gating would have requires undue experimentation. The Examiner made a finding from Howk et al. that "some host molecules have small portals that preclude guest or solvent passage through the molecule into the interior of the particle, other hosts have large portals that are not readily influence and fail to form any stable complex with the guest molecule, and finally, some host molecules have small portals that admit guest molecules only under specific solvent conditions." The Examiner has not explained how and why this finding would cause undue experimentation with respect to the non-plant or animal virion coat protein shells of the invention.

Each of the Declarants Zlotnick, Smith and Johnson refer to the Declaration of Michael J. Young, Declarants Zlotnick, Smith and Johnson state:

> The Declaration of Dr. Young provides the results of additional experiments which indicates that structures of more than 30 viruses have been determined to atomic resolution and that these structures reveal that the coat protein subunits of

> all virions are assembled and stabilized by non-covalent bond interactions such as H bonding ionic interactions and hydrophobic interactions. Further, Dr. Young's Declaration states that the vast majority of icosahedral viruses have a coat protein subunit that utilizes a 8-stranded anti-parallel, β-barreled fold, commonly termed the "β barrel jelly roll fold", which protein fold is dominant across all taxmomic classes of virus regardless of host. Dr. Young then lists various viruses CCMV, the human viruses Norwalk virus, Polio virus, Rhino virus, Parvo virus and Flockhouse virus which have this protein fold as the predominant structural feature. Dr. Young then presents evidence as having synthesized a paratungstate polymer using the virions protein cage of an animal Noralk [sic, Norwalk] virus (NWV) having icosheidral geometry and a constrained reaction vessel. Dr. Young also presents evidence of encapsulation of paratungstate within CCMV, and encapsulation of polyanetholesulfonic acid within CCMV, encapsulation of iron oxides within CCMV. Dr. Young then concludes that every system studied by the inventors has meet with success with only minor modifications being required in some cases. [Zlotnick, p. 6, ¶ 10; Smith, p. 7, ¶ 10; and Johnson, p. 7, ¶ 10.]

There is no evidence of record to cast doubt on the truthfulness of the statements made by the declarants. According to Declarant Young, the predominant structural feature defining the protein shell referred to above by Declarants Zlotnick, Smith and Johnson, "may ultimately account for our observations to date revealing the broad capacity of viral capsids to act as constrained reaction vessels for mineralization and/or entrapment of inorganic, organic and metallo-organic substances" (Young Declaration, p. 3, ¶ 4). Since the structure set forth above appears to transcend plant and non-plant virion coat protein shells, persons having ordinary skill in the art would have expected an animal protein to exhibit the same encapsulation property as the CCMV virus. Applicants have presented evidence by persons skilled in the art, namely, the Declarations by Zlotnick, Smith and Johnson, that establish that following the teachings of the present disclosure, a person having ordinary skill in the art could practice the invention with non-plant virions without undue experimentation. There is no evidence of record or reasoning

presented in the rejection of record that that would cast doubt on the truthfulness of statements made by Declarants Young, Zlotnick, Smith and Johnson.

Also as discussed, *supra*, the absence of a working embodiment or example is considered in determining non-enablement, but the absence of a working embodiment is not necessary to establish enablement. The evidence of record establishes that it is the structure of the virion that governs encapsulation, and not its type, i.e., whether the virion is a plant virion or an animal virion, a person having ordinary skill in the art, as evidenced by the Declarations of Zlotnick, Smith and Johnson, would have found the plant virion working example sufficient to lead one to expect that the invention can be practiced using a non-plant virion in place of the plant virion without undue experimentation.

For reasons already discussed, *supra*, the Examiner has not established that the state of the art or level of skill in the art at the time of the effective filing date of the present application. The Examiner has not established the relative skill of those in the art at the time of the effective date of the application. The Declarations of Zlotnick, Smith and Johnson, who are persons skilled in the art, establish the skill in the art. According to these persons, a person having ordinary skill in the art would have expected that the invention could be practiced using non-plant virions without undue experimentation. The Examiner dismisses the Declarations of Zlotnick, Smith, Johnson, Young and Douglas as failing to "to provide any data addressing the various caveats raised in the rejection." The Declarations were not presented to provide data, but to express opinions as persons skilled in the art regarding statements made by the Examiner during prosecution. Opinion evidence presenting facts to support a basis for deciding that a specification complies with the requirements of under 35 U.S.C. § 112, first paragraph, is entitled

to consideration and some weight with respect to issue. See Section 716.01(c) of the *Manual of Patent Examining Procedure.* Accordingly, the Examiner's summary dismissal of the declarations is in error.

As for the Young Declaration, the Examiner dismisses this declaration on the ground that the declaration "failed to provide a use for said nanoparticle," and therefore, "it is not readily manifest if this example constitutes a full working embodiment." This summary dismissal of the declaration is in error. The Declaration presents clear evidence that counters the Examiner's position that preparing virion-constrained nanoparticles using animal virions is not enabled by the disclosures in the present specification.

For all of the foregoing reasons, the specification is enabling and a person having ordinary skill in the art would have been able to practice the claimed inventon, without undue experimentation, following the teachings of the specification in the present application. The Examiner has not established a *prima facie* case that the disclosure of the present invention is non-enabling with respect to the claimed subject matter. The determination of lack of enablement is fact dependent. On the present record, the Examiner has not presented numerous conclusionary statements, but insufficient factual findings to establish that the disclosure does not satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. Accordingly, it is respectfully requested that the rejection be reversed.

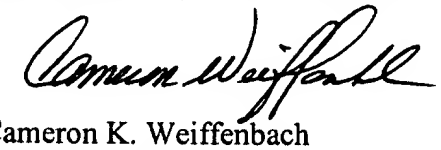
Conclusion

For the foregoing reason, Appellants submit that the Examiner has failed to establish that the inventors of the claimed invention were not in possession of the invention at the time the patent application was filed and that undue experimentation would be required to practice the

claimed invention. Accordingly, the rejections of the appealed claims under the first paragraph of 35 U.S.C. § 112 are improper and should be reversed.

Sincerely yours,

McDERMOTT, WILL & EMERY



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